REMARKS

Claims 1-19 and 29-40 are currently pending and under examination in the application, with claims 1, 29, 34 and 35 being independent. Claims 20-28 and 41-49 have been withdrawn from consideration. Claims 2, 16, and 37 have been canceled. Claims 1, 17, 29, and 33-35 have been amended. Applicants submit that no new matter has been added by the way of these amendments. Consideration of the amendments and remarks included herein is respectfully requested.

I. Enablement Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner maintains the rejection of claims 1-19 and 29-40 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable the method of treating, preventing, or ameliorating multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18, or other disorders associated with an IL-10 deficiency by administering to a subject an agonist of IL-21/IL-21R. (*Office Action,* dated August 10, 2007, at p. 3). Specifically, the Examiner alleges that the specification does not enable (1) an agonistic anti-IL-21R antibody, as well as an antigen-binding fragment of the agonistic anti-IL-21R antibody, (2) an IL-21 polypeptide with at least 90% identity to SEQ ID NO:2, and (3) a method of treating, preventing, or ameliorating a disease using an agonist of IL-21/IL-21R. (*Id.*, at pp. 3-6). For the following reasons, Applicants respectfully disagree.

(1). Agonistic Anti-IL-21R Antibody

Regarding the enablement rejection of an agonistic anti-IL-21R antibody, the Examiner alleges that although the generation of an antibody is routine in the art, an antibody with agonistic activity requires the knowledge of the specific epitopes required for binding of an agonistic antibody to IL-21R. (*Id.*, at p. 4). The Examiner also contends that enablement is not based on the guidance of how to screen, but rather on how to make and use.

Applicants reiterate that the requirement of some experimentation or even extensive experimentation does not necessarily invalidate a claim under § 112, especially if such experimentation is routine. (See, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). "The key word is 'undue,' not 'experimentation.'" (*In re Wands*, 858 F.2d at 736-7 (quoting, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974))). Accordingly, trial-and-error may be acceptable and will not render a claim invalid if the experimentation is routine or the specification provides a reasonable amount of guidance. (See, *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal...")). MPEP §2164.01 teaches that "[a] key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biochemical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening."

Applicants submit that they have provided sufficient guidance for how to easily make and screen for agonistic antibodies to IL-21R. Applicants teach how to make polyclonal and monoclonal antibodies to IL-21R (See, e.g., *Specification*, at ¶¶ [0100]-[0102]). Additionally, one skilled in the art would know how to test whether these antibodies bind IL-21R (by using, e.g., a well-known ELISA assay). Thus, making antibodies against IL-21R is routine.

One skilled in the art would also know how to test whether an antibody to IL-21R is an agonistic antibody. For example, a skilled artisan would know to use, e.g., the experimental protocol of the Example entitled "Proliferative Response and Cytokine Production Induced by Murine IL-21" on pages 49-51 of the specification to culture lymphocytes with an IL-21R antibody and determine whether the antibody is capable of inducing the same reaction or activity typically produced by IL-21. The specification also teaches that agonists of IL-21/IL-21R can be screened for binding and/or activation of an IL-21R polypeptide using procedures known in the art. (Specification, at ¶ [0010]). Thus, determining whether an anti-IL-21R antibody is an agonist is also routine. Therefore, even if, *arguendo*, having obtained a number of anti-IL-21R antibodies, a skilled artisan would be required to conduct extensive screening, such screening is not undue because the starting materials necessary to make the invention are available. (See MPEP §2164.01).

Applicants respectfully submit that, contrary to the Examiner's assertion, agonistic antibodies do not require the knowledge of specific epitopes for binding to IL-21R. What is required is simply determining that in an appropriate assay, e.g., an assay of the Example entitled "Proliferative Response and Cytokine Production Induced by Murine IL-21" on pages 49-51 of the specification, an anti-IL-21R antibody is capable of inducing the same responses as the IL-21 polypeptide, e.g., inducing IL-10 production, etc. Thus, Applicants respectfully submit that they have enabled the methods of using agonistic anti-IL-21R antibodies.

Moreover, Applicants submit that they have also enabled the methods of using antigen-binding fragments of the agonistic anti-IL-21R antibodies. Applicants teach that the binding fragments encompassed within the term "antigen-binding fragment" include (i) an Fab fragment, (ii) an $F(ab')_2$ fragment, (iii) an Fd fragment, (iv) an Fv fragment, (v) a dAb fragment,

or (vi) a CDR. (*Specification*, at ¶[0099]). The specification also teaches that "[t]hese antibody fragments are obtained in the same manner as are intact antibodies using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies." (*Id.*). For instance, once a skilled artisan obtains an agonistic anti-IL-21R antibody, he/she can use well-known proteases, e.g., papain and pepsin, to generate, e.g., Fab and $F(ab')_2$ fragments, respectively. Moreover, the extent of the CDR regions has been precisely defined. (*Id.,* at ¶ [0095], citing Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. et al. (1987) *J. Mol. Biol.* 196:901-917). Thus, Applicants respectfully submit that they have also enabled using antigen-binding fragments of the agonistic anti-IL-21R antibodies for the claimed use.

(2). IL-21 Polypeptide with at Least 90% Identity to SEQ ID NO:2

The Examiner alleges that the specification does not enable an IL-21 polypeptide with 90% identity to SEQ ID NO:2 (as in claim 2) because the specification does not teach what amino acids need to be conserved and what amino acids could/could not tolerate modification. (*Office Action*, at p. 5). The Examiner also alleges that a single amino acid change can abolish ligand binding to the receptor. (*Id.*). Applicants respectfully disagree with the Examiner's assertions. However, solely to expedite prosecution of the application, Applicants presently cancel claim 2 without prejudice. Thus, Applicants respectfully submit that Examiner's rejection is inapposite.

(3). Method of Treating, Preventing, or
Ameliorating a Disease Using an Agonist of IL-21/IL-21R

The Examiner alleges that the specification is not enabling for the method of treating, preventing, or ameliorating MS or a symptom of MS or other disorders. (*Office Action*, at p. 6). The Examiner also alleges that because the specification describes several diseases that are associated with an IL-10 deficiency, the evaluation of an IL-10 parameter is not indicative of MS, and that it is unclear what IL-10 activity is encompassed within the term "IL-10 parameter." (*Id.*, at p. 7). Applicants respectfully disagree.

In order to expedite prosecution of the present application, Applicants have amended claims 1, 17, 29, and 33-35. Applicants respectfully submit that the specification teaches a method of treating or ameliorating MS or other claimed disorders, or a symptom thereof, by administering an agonist of IL-21/IL-21R. As previously discussed by Applicants, treating EAE in mice reasonably correlates with treating MS in humans. (Amendment dated May 14, 2007, at pp. 22-25). Applicants have demonstrated in the Examples that treating mice with IL-21 leads to a decrease in the severity of EAE. (See, e.g., Example entitled "Development of EAE in Mice Treated with IL-21", ¶¶ [0171]-[0176]). Thus, Applicants have taught a method of treating or ameliorating EAE and, by correlation, a method of treating and ameliorating MS (or a symptom of MS), by administering an agonist of IL-21/IL-21R. As amended, Applicants' claims are directed to methods of treating or ameliorating IL-10-associated disorders. Because an IL-21 agonist is capable of modulating IL-10 production, the specification teaches that the invention features a method of treating or ameliorating an IL-10-associated disorder by administering an agonist of IL-21/IL-21R. (*Specification,* at ¶ [0025] and Table 2). Thus, Applicants respectfully submit that they have enabled a method of treating or ameliorating MS, or a symptom of MS, and other disorders associated with an IL-10 deficiency.

With regard to the Examiner's contention that what is encompassed within the term "IL-10 parameter" is unclear, Applicants respectfully submit that the specification clearly describes "IL-10 parameter" throughout the specification, for example at paragraphs [0014] and [0028]. Additionally, original claim 36 recites that "IL-10 parameter" comprises quantitative information about levels of IL-10 protein or IL-10 mRNA. The specification also teaches when and how to measure and evaluate an IL-10 parameter, e.g., before and after administration of an IL-21/IL-21R agonist. (See also the Examples, especially the Example entitled "Proliferative Response and Cytokine Production Induced by Murine IL-21"). Thus, Applicants respectfully submit that a skilled artisan would know to measure and evaluate an IL-10 parameter, such as IL-10 protein or IL-10 mRNA levels, for use an as indicator of the status of MS or another IL-10-associated disorder.

For at least these reasons, Applicants respectfully submit that the instant claims are enabled, and respectfully request withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph.

II. Written Description Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner maintains the rejection of claims 1-3, 29-30, and 34-40 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. (*Office Action*, at pp. 7-9). The Examiner alleges that Applicants did not adequately describe a genus of agonists of IL-21/IL-21R, a genus of IL-21 polypeptides with at least 90% identity to SEQ ID NO:2, and a genus of antigen-binding fragments of the agonistic anti-IL-21R antibody. Applicants respectfully disagree.

Regarding the genus of IL-21/IL-21R, Applicants respectfully submit that they teach that the agonist of the IL-21/IL-21R is selected from the group consisting of IL-21 polypeptide, an agonistic anti-IL-21R antibody, or an antigen-binding fragment of an agonistic anti-IL-21R antibody. Applicants define IL-21 polypeptide as a protein which is capable of interacting with, e.g., binding to, IL-21R. (*Specification*, at ¶[0048]). An example of human IL-21 polypeptide is represented in SEQ ID NO:2, and an example of mouse IL-21 polypeptide is represented in SEQ ID NO:4. Thus, Applicants respectfully submit that they were in possession of the IL-21 polypeptide.

Applicants disagree with the Examiner's allegation that Applicants do not adequately describe a genus of IL-21 polypeptides with at least 90% identity to SEQ ID NO:2. However, solely to expedite prosecution of the Application, Applicants presently cancel claim 2 without prejudice. Therefore, Applicants respectfully submit that the Examiner's rejection is moot.

Applicants also disagree with the Examiner's allegation that they have not adequately described a genus of agonistic anti-IL-21R antibody. Applicants describe that IL-21R protein can be used to immunize animals to obtain anti-IL-21R antibodies, and that antibodies can be screened for agonistic anti-IL-21R activity using procedures well known in the art. Thus, Applicants submit that they have disclosed sufficient identifying characteristics of agonistic anti-IL-21R antibodies so one of skill can "visualize or recognize the identity" of the invention. (See, *Regents of the University of California v. Eli Lilly, Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997), stating that to satisfy the written description requirement, a chemical compound, such as gene or protein, must disclose sufficient identifying characteristics to allow one skilled in the art to "visualize and recognize the identity" of the invention).

Additionally, Applicants also teach what is encompassed by the term "antigen-binding fragment" of an antibody, and give various examples of the antigen-binding fragments of an antibody, e.g., Fab fragment, $F(ab')_2$ fragment, Fd fragment, etc.. (*Specification*, at ¶ [0099]). Applicants teach that antibody-binding fragments can be made using conventional techniques known to one skilled in the art. (*Id.*). Thus, Applicants respectfully submit that based on their disclosure, one skilled in the art would also be able to "visualize or recognize the identity" of the antigen-binding fragments of the agonistic anti-IL-21R antibodies.

For at least these reasons, Applicants respectfully submit that they have provided adequate written description to show that they were in possession of the claimed invention, and respectfully request withdrawal of the 35 U.S.C. § 112 written description-based rejection of the claims.

III. Indefiniteness Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 16-19 and 34-40 as indefinite, alleging that although different activities of IL-10 have been shown in the art, it is not clear what specific activity of IL-10 can be determined and used in the claimed method. (*Office Action*, at pp.9-10). Although Applicants disagree with the Examiner, Applicants presently amend claims 17 and 34, and cancel claims 16 and 37 in order to expedite prosecution of the application. Thus, Applicants respectfully submit that Examiner's rejection is moot, and respectfully request withdrawal of the indefiniteness-based rejection of the claims.

IV. Rejection Under 35 U.S.C. § 102

The Examiner rejects claims 1-4, 9-12, 14, and 29-34 under 35 U.S.C. § 102(e) as allegedly anticipated by Novak et al. (U.S. Patent Application No. 6,605,272; "the '272 patent"). The Examiner alleges that the '272 patent teaches the therapeutic use of IL-21 (Zalpha11 ligand) in several immunological disorders including MS. (*Id.*, at p. 11). The Examiner also alleges that the '272 patent teaches that IL-21 enhances proliferation of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells and regulates production of cytokines, such as increasing IL-10 and decreasing IFN-γ. (*Id.*). The Examiner further alleges that the limitation of ameliorating a symptom of MS, or MS associated with an IL-10 deficiency, would be an inherent result of regulating T cell proliferation and cytokine production by administration of IL-21. (*Id.*). Applicants respectfully disagree with the Examiner's assertions.

In order to anticipate a claim, a reference must teach every element of that claim. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); see also MPEP §2131. The Examiner bears the burden of demonstrating that a reference teaches every element of a claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Moreover, in order to anticipate the claim, the claim disclosure must be enabling. MPEP §2121, citing *In re Hoeksema*, 399 F.2d 269 (CCPA 1968). Thus, in order to anticipate the claims, the '272 patent must teach a method of treating or ameliorating MS or an immunological disorder associated with an IL-10 deficiency (or increased IFN-γ), and must contain an enabling disclosure of such teaching.

Applicants respectfully submit that the '272 patent does not teach the method of treating or ameliorating MS or an immunological disorder associated with an IL-10 deficiency (or increased IFN-γ), and does not provide enabling disclosure for such method. First, the '272

patent teaches that diseases such as MS "are the result of a complex network of immune dysfunction." (The '272 patent, at column 42, lines 9-31). Thus, the '272 patent teaches that "zalpha11 Ligand (or an antagonist of the Ligand) that can be used to manipulate more than one type of immune cell is an attractive therapeutic candidate for intervention at multiple stages of disease." (*Id.*). Thus, the '272 patent does not teach whether it is an agonist or an antagonist of IL-21 that is useful in a method of treating or ameliorating MS or other IL-10-associated disorder.

Moreover, Examples 41 and 42 of the '272 patent (cited by the Examiner) do not teach the use of IL-21 in treating or ameliorating MS or immunological disorder associated with an IL-10 deficiency (or increased IFN-γ). Example 41 of the '272 patent teaches the role of zalpha11 in NK cells, a cell type with unclear significance in MS. Example 42 of the '272 patent simply explores the effect of zalpha11 on T cell proliferation. In fact, nowhere does the '272 patent associate IL-21 with the modulation of IL-10 (or IFN-γ), let alone teach the use of an IL-21/IL-21R agonist to treat or ameliorate a symptom(s) of MS or any other IL-10-associated disorder(s).

Further, the Examiner has not satisfied the required burden of providing the evidence tending to show that the method described in the present claims is inherently present in the '272 patent. Regarding inherency, MPEP § 2112 states:

> [t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized

> by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Thus, in order to demonstrate inherency, the Examiner must show that the method of treating or ameliorating MS or an immune disorder associated with an IL-10 deficiency (or increased IFN-γ) by administering the IL-21/IL-21R agonist is necessarily present in the '272 patent. The fact that the '272 patent discloses that IL-21 may affect the proliferation of certain immune cells, does not mean that the '272 patent also teaches IL-21-mediated regulation of cytokines, particularly IL-10 (and IFN-γ). Therefore, the '272 patent cannot possibly inherently disclose the method of the instant claims, namely the use of an IL-21/IL-21R agonist to prevent or ameliorate the symptoms of MS or other IL-10-associated disorders.

For at least these reasons, Applicants respectfully submit that the '272 patent does not, either expressly or inherently, anticipate the instant claims, and request withdrawal of the anticipation-based rejection under 35 U.S.C. § 102.

V. Rejection Under 35 U.S.C. § 103

(1). Rejection Under 35 U.S.C. § 103(a) over the '272 Patent in View of the '549 Application and Kawai

The Examiner rejects claims 1-15 and 29-34 under 35 U.S.C. 103(a) as allegedly obvious over the '272 patent in view of Carter et al. (U.S. Patent Application No. 2003/0108549; "the '549 application") and Kawai et al. ((1996) *Cell Immunol.* 171:262-68; "Kawai"). The Examiner alleges that Novak teaches the limitations of claims 1-4, 9-12, 14, and 29-34 of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency. (*Office Action,* at pp. 12-15). The Examiner also alleges that although the '272

patent does not teach agonistic anti-IL-21R antibodies, the '549 application teaches an agonistic anti-IL-21R antibody. (*Id.*, at p. 13). In addition, the Examiner contends that the '549 application teaches a combination of anti-inflammatory agents and anti-IL-21/IL-21R agonists, and that an IL-21/IL-21R agonist enhances T cell proliferation and cytokine regulation. (*Id.*). Finally, the Examiner alleges that although the '272 patent and the '549 application do not teach injection of IL-21 agonists into CNS, Kawai teaches intracerebroventricular and intrathecal administration routes. (*Id.*). Applicants respectfully disagree with the Examiner.

According to MPEP § 2143, in order to establish a prima facie case of obviousness, the prior art references, when combined, must teach or suggest all of the claim limitations. Thus, in order to render the instant claims obvious, the combination of the '272 patent, the '549 application and Kawai must teach all of the limitations of the instant claims. Additionally, there must exist a motivation to combine the references, and a reasonable expectation of success upon doing so. (MPEP § 2143).

As Applicants explained above, the '272 patent does not teach the claim limitation of treating or ameliorating MS or an immunological disorder associated with an IL-10 deficiency (or increased IFN-γ) by administering an agonist of IL-21/IL-21R. Applicants respectfully reiterate that the '272 patent teaches that diseases such as MS "are the result of a complex network of immune dysfunction." (The '272 patent, at column 42, lines 9-31). Additionally, the '272 patent does not associate IL-21 with the modulation of IL-10 (or IFN-γ), nor does it teach or suggest that an IL-21/IL-21R agonist would be useful to treat or ameliorate MS (or a symptom of MS) or any other IL-10-associated disorder.

In light of at least the aforementioned disclosure of the '272 patent, one would not be motivated to combine these teachings with those of the '549 application and Kawai to reach

the claimed invention. Therefore, Applicants respectfully submit that independent claims 1 and 29, and claims 3-15 and 30-34, which depend therefrom, are not obvious under 35 U.S.C. §103(a) over the '272 patent in view of the '549 application and Kawai.

(2). Rejection Under 35 U.S.C. §103(a) over the '272 Patent in View of the '549 Application and Kawai, Further in View of Beebe

The Examiner also alleges that claims 1-19 and 29-40 are obvious over the '272 patent in combination with the '549 application and Kawai, further in view of Beebe et al. ((2002) *Cytokine and Growth Factor Rev.* 13:403-12; "Beebe"). (*Office Action*, at pp. 15-16). The Examiner alleges that the '272 patent teaches the therapeutic use of IL-21 in immunological disorders including MS, the '549 application teaches enhancement of T cell proliferation and cytokine regulation by an IL-21/IL-21R agonist, Kawai teaches intracerebroventricular and intrathecal administration of monoclonal antibodies in an MS animal model, and Beebe teaches that the level of IL-10 is low in MS and is increased after treatment of the disease. (*Id.*, at p. 16). Thus, the Examiner alleges that the instant claims are obvious. For the following reasons, Applicants respectfully disagree.

As discussed above, the '272 patent does not teach treating or ameliorating MS or an immunological disorder associated with an IL-10 deficiency (or increased IFN-γ) by administering an agonist of IL-21/IL-21R, and one would not be motivated to combine the teachings of the '549 application and Kawai with those of the '272 patent to reach the claimed invention. Beebe does not cure this deficiency. Although Beebe teaches that the level of IL-10 in MS patients is low, it does not provide a nexus between IL-21 agonism and the treatment of MS or immunological disorders. Therefore, Beebe does not provide a motivation and

expectation of success in treating or ameliorating MS or immunological disorders associated with an IL-10 deficiency by administering an agonist of IL-21/IL-21R.

For at least these reasons, Applicants respectfully submit that the instant claims are not obvious over the combination of the '272 patent, the '549 application, and Kawai, further in view of Beebe; and respectfully request withdrawal of the obviousness-based rejections of the claims.

VI. New Rejections Under 35 U.S.C. §112

(1). New Matter Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner has rejects claims 1-19 and 29-40 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that Applicants did not disclose that multiple sclerosis is associated with increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, and increased IL-18. (*Office Action*, at p.p. 17-18). Applicants respectfully traverse the rejection.

Solely to expedite prosecution of the application and without prejudice, Applicants amend the claims to recite a method of treating or ameliorating multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ by administering to a subject an agonist of IL-21/IL-21R. Applicants submit that they have disclosed that MS is associated with increased IFN-γ.

It is well known in the art that MS and EAE are associated with imbalance of Th1 and Th2 cytokines, wherein the production of Th2 cytokines (e.g., IL-10) is decreased and the production of Th1 cytokines (e.g., IFN-γ) is increased. (See, e.g., Aharoni et al. (1997) *Proc. Natl Acad. Sci. USA* 94:10821-26, previously presented). Thus, one skilled in the art would

know that MS may be associated with increased IFN-γ. Moreover, Applicants specifically teach that treatment of lymphocytes derived from EAE mice with IL-21 resulted in a decrease in IFN-γ as compared to controls, while treatment of lymphocytes with IL-21R resulted in an increase in IFN-γ. (See, e.g., Fig. 3 and Example entitled "Proliferative Response and Cytokine Production Induced by Murine IL-21"). Thus, Applicants respectfully submit that a method of treating or ameliorating a symptom of multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ by administering to a subject an agonist of IL-21/IL-21R is disclosed and taught in the specification.

For at least these reasons, Applicants respectfully request withdrawal of the new matter written description-based rejection of claims 1-19 and 29-40.

(2). Indefiniteness Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner also rejects claims 1-19 and 29-40 under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*Office Action*, at pp. 18-19). Specifically, the Examiner alleges that the claims are indefinite because they recite "a symptom of multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, and increased IL-18," and the disclosure fails to set the metes and bounds of what is encompassed within such symptom. (*Id.*). Applicants respectfully disagree.

Applicants teach that "treatment of mice prophylactically with an IL-21/IL-21R agonist, e.g., murine IL-21 polypeptide, results in an amelioration of symptoms in mouse models for experimental autoimmune encephalomyelitis (EAE)." (*Specification,* at ¶ [0006]; see also Fig. 5 and Table 5). Specifically, the specification teaches that such symptoms include: limp tail,

hind limb weakness or partial paralysis, complete hind limb weakness or partial paralysis, and front and hind limb paralysis. (*Id.*, at ¶ [0163]). The specification also teaches a number of exemplary symptoms of multiple sclerosis, such as tremor and difficulty walking. (*Id.*, at ¶¶ [0007] and [0130]). Because Applicants teach (1) a number of symptoms associated with MS, (2) that EAE is a rodent model of multiple sclerosis, and (3) that treatment of EAE mice with an agonist of IL-21/IL-21R can reduce symptoms of EAE, Applicants respectfully submit that the recitation "a symptom of multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ" is adequately described in the specification.

For at least these reasons, Applicants respectfully request withdrawal of this indefiniteness-based rejection of claims 1-19 and 29-40.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns and rejections have been answered and overcome, and that the subject matter of the presently claimed invention satisfies the requirements of 35 USC § 112 and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

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